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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,657	05/04/2001	Harry M. Meade	GTC-21	9001

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/849,657	MEADE ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *see attached*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1/16/02,9/21/04,12/13/04

This Application, filed May 4, 2001, claims priority to U.S. Provisional Application, filed May 5, 2000.

Claims 1-24 are pending.

Election/Restrictions

Applicants' election with traverse of Group II (claims 10-18) in the reply filed on December 14, 2004 is acknowledged. The traversal is on the ground(s) that the method of Group II claims is particularly well suited to use in conjunction with the "apparatus"- the transgenic animal, of Group III, and that a search of Group II claims would necessarily cover the animal recited in the Group III claims. The Examiner has considered the arguments and will rejoin Groups II and III.

Applicants have cancelled claims 1-9 and 20-24. Claims 10-19 are under consideration in this Office Action.

Information Disclosure Statement

The information in the articles has been considered but a replacement copy of the December 13, 2004 IDS with correct spelling and information is required. With regards to the incorrect information, on page 12/12 of the December 13, 2004 IDS, Colowick is not the author of the Methods in Enzymology article. On page 12/12 of the December 13, 2004 IDS, the article by White is missing a year.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10-13, 16-19 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 10-13, 16-19 are to a transgenic organism. This claim encompasses human, which is a non-statutory matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of making milk comprising transgenic human decorin, obtained from a transgenic mouse comprised of an expression cassette of a goat beta-casein promoter operably linked to the nucleotide sequence encoding human decorin, and for a method of making transgenic human decorin in E. coli, S. cerevisiae, and S. pombe and obtaining a preparation from E. coli, S. cerevisiae, and S. pombe, does not reasonably provide enablement for a method of making any preparation of any transgenic decorin, wherein any preparation comprising any transgenic decorin is obtained from any transgenic organism comprising any transgene that directs expression of decorin or from any product produced by said organism. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The instantly claimed invention is drawn to a method of making a preparation comprising transgenic human decorin, wherein said decorin is obtained from a transgenic organism or from a product of the transgenic organism. However, the claimed invention is not enabled because the specification as filed fails to provide sufficient guidance for how to make and use the claimed method and an artisan of skill

would require undue experimentation to make and use the method as recited because the art of treating a disease associated with VEGF was unpredictable at the time of filing.

Unpredictability occurs with regards to a method of making any preparation comprising any transgenic decorin, wherein any preparation of any transgenic decorin is obtained from any transgenic organism comprising of any transgene that directs expression of decorin or from any product produced by said organism.

With regards to a method of making any preparation, the art at the time of filing teaches that are many different ways to make a preparation. A method for making a preparation could encompass way the protein of interest is administered or stored. The art at the time of filing teaches that there are many different ways to administer protein to a patient, for example, i.v., i.p., orally, subcutaneously, and topically. However, the route of administration depends on the ability of the protein to reach its target and thus, while some proteins may be administered one way, another set may be administered using a different route. Each route of administration needs to be determined empirically for every protein. In the case of storage, proteins can be suspended in a buffer. Depending on the protein, buffer conditions can vary from protein to protein. The art has shown that proteins are generally unstable and proteolytic inhibitors are usually added to the proteins in buffer. In other cases, however, the art has shown that proteolytic inhibitors sometimes inhibit the activity of proteins. As illustrated by these situations, the art teaches that the conditions used to store a protein of interest are determined empirically. Determining how decorin could be stored or prepared in a

pharmaceutical composition is unpredictable and would involve undue experimentation. The specification as filed does not provide sufficient guidance, working examples, and evidence as to how an artisan of skill would make other preparations of transgenic decorin.

With regards to the method of making any preparation comprising any transgenic decorin, at the time of filing, the art of record teaches that expressing proteins is unpredictable because a protein's ability to function and to be soluble depends on whether a protein folds appropriately. Further, the art teaches that a protein's ability to function also depends on its post-translational modification. Because the art teaches that folding is unpredictable and making soluble, functional proteins is determined empirically, the specification as filed does not provide sufficient guidance, working examples and evidence as to how an artisan of skill would have made and used the claimed invention commensurate with the scope of the claims without undue experimentation. For this reason, the specification is not enabled for any protein other than human decorin.

With regards to the method of making a preparation of any transgenic decorin obtained from any transgenic organism comprising any transgene that directs expression of decorin, the art teaches that the making of a transgenic construct and transgenic organism is empirically determined. With regards to the transgenic construct, the transgenic construct is primarily comprised of a nucleic acid sequence encoding a gene of interest operably linked to a promoter. The art has also shown that while one promoter has activity in one organism, that same promoter may not have any

activity in another organism. Thus, whether or not a promoter has activity in an organism must be determined empirically.

With regards to the transgenic organisms, the art has shown that while there is predictability in making transgenic yeast and bacteria, there is unpredictability in making transgenic plants and animals. With regards to fungi, the art shows that S. cerevisiae and S. pombe has been demonstrated to express recombinant protein. However, it is not known in the art how to express recombinant protein in other species of yeast or in other fungi, such as mushrooms. For this reason, there is enablement for S. cerevisiae and S. pombe, but not for other fungi or yeast. With regards to bacteria, the art teaches that E. coli have been demonstrated to express recombinant protein. However, it is not known how to express recombinant protein in other species of bacteria. For this reason, there is enablement for E. coli, but not for other bacteria. There is relative ease in creating transgenic E. coli, S. cerevisiae, and S. pombe because transgene maintenance in yeast and bacteria do not require that the transgene be integrated into the chromosome.

In contrast, making a transgenic plant and animal is unpredictable. This is because the method of making either of these two types of organisms depend on chromosomal integration of the transgene construct. According to Mullins and Mullins (1996, J. Clin. Invest, 97: 1557-1560), pronuclear injection, the method used to generate transgenic nonmurine animals, is unreliable, as there is low efficiency of gene integration (page 1557, second column, first full paragraph, lines 7-8). Furthermore, Mullins and Mullins state that the major problem regarding pronuclear microinjection is,

"that the exogenous DNA integrates randomly into chromosomal DNA. Position effects, where the transgene is influenced by its site of integration in the host chromosome, can have major consequences on the expression of the transgene, including loss of cell specificity, inappropriately high copy number--independent expression and complete silencing of the transgene (page 1557, column 2, second paragraph, line1 to page 1558, first column, first paragraph, lines 1-6)." It should be pointed out that Mullins and Mullins' review was written with a mammalian scope in mind. Pronuclear injection, the method described in the specification, does not work in non-mammalian species such as amphibians, fish, reptiles, birds and insects. Despite this, it should be pointed out that to generate transgenic amphibians, fish, reptiles, birds, insects, and plants, a skilled artisan would need to integrate the transgene into the chromosome of the host. The specification as filed does not provide sufficient guidance, working examples and evidence as to how an artisan of skill would have made and used the claimed invention commensurate with the scope of the claims without undue experimentation. For this reason, the specification is not enabled for any transgenic organism other than mouse.

In light of the fact that because making transgenic plants and animals is unpredictable, it would then follow that obtaining any product produced by the transgenic plant or animal as not being enabled. However, as described above, it is possible to obtain transgenic human decorin from E. coli, S. cerevisiae, and S. pombe. In terms of "obtaining" decorin from E. coli, S. cerevisiae, and S. pombe, the art has shown that decorin could be purified from bacteria. Hering et al. (1996, Analytical Biochemistry, 240: 98-108) teaches that bovine decorin made by bacteria requires a

solubilization step. Bovine decorin is insoluble and is contained within inclusion bodies. Bovine decorin was solubilized in GdnHCl and refolded by simultaneous dilution of the protein and chaotrope to minimally denaturing conditions followed by disulfide shuffling (page 103, first column, second paragraph, lines 1-5; see also Figure 4). This example shows that obtaining decorin was possible. However, the specification does not teach methods to extract decorin from any product produced by transgenic plants and animals, such as from leaves of a plant or from the skin of an animal. For this reason, the specification is not enabled for decorin obtained from any product from a plant or animal.

In view of the lack of guidance, working examples, breadth of the claims, the nature of the invention, and the unpredictability of the art, it would have required undue experimentation to make and/or use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Hering et al. (1996, Analytical Biochemistry, 240: 98-108).

Claim 10 is to a method of making a preparation of transgenic decorin comprising providing a transgenic organism with a transgene which directs the expression of decorin, allowing the transgene to be expressed, and recovering a preparation of transgenically produced decorin from the organism or from a product produced by the organism.

Hering et al. teach how to express bovine decorin in bacterial cells. The nucleotide sequence encoding bovine decorin was inserted into an expression vector pMal-c (page 100, first column, lines 20-21). The vector was then transformed into *E. coli* TB-1, TOPP, or XL1-blue cells, grown in culture, and induced with IPTG. Bacteria were then lysed (page 101, first column, first paragraph under "Preparative Induction, Refolding, and Purification of MBP-Decorin," lines 14-21), the inclusion bodies were dissolved (page 101, first column, first paragraph under "Preparative Induction, Refolding, and Purification of MBP-Decorin," lines 25-28), and the protein was renatured (page 101, first column, second paragraph under "Preparative Induction, Refolding, and Purification of MBP-Decorin," to second column, first three paragraphs).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houdebine et al. (U.S. Patent 5,965,788, patented October 12, 1999) in view of Krusius and Ruoslahti (PNAS, USA, 83:7683-7687, see IDS), Mann et al. (1990, JBC, 265: 5317-5323), and Roberts et al. (1992, Gene, 121: 255-262).

Houdebine et al. teach a method of preparing a protein of interest in the milk of a transgenic animal. Houdebine et al. teach that the milk-expressed transgenic protein is abundant in supply and tends to be properly post-translationally modified. In this method, Houdebine et al. teach that a transgenic construct, pW3, comprising the promoter of the rabbit WAP gene operably linked to the nucleic acid sequence encoding human growth hormone (Houdebine et al., col. 6, lines 56-58) and the transgenic construct, pJ4, comprising the promoter of the rabbit WAP gene operably linked to the nucleic acid sequence encoding bovine growth hormone (Houdebine et al., col. 6, line 66 to col. 7, line 2) were injected into the male pronucleus of mouse embryos (Houdebine et al., col. 7, lines 16-18). Transgenic mice were evaluated for the presence of the transgene by Southern blotting and by evaluating the concentrations of growth hormone in the blood and milk via specific radioimmunological assays (Houdebine et al., col. 7, lines 25-30). Houdebine et al. teach that by specific radioimmunological tests, mice comprised of the pW3 construct produced 10-21 mg/ml of human growth hormone. Mice comprised of the pJ4 construct produced from 5-17 mg/ml of bovine growth hormone. While Houdebine et al. teach that human and bovine growth hormone were expressed at high levels in mice, they do not teach that decorin was expressed, nor do they teach the promoter of goat beta-casein.

Krusius and Ruoslahti (1986, PNAS, USA, 83; 7683-7687) teach the nucleotide and amino acid sequences of human decorin (page 7684, second column, first and second paragraphs under "cDNA Sequence and Inferred Amino Acid Sequence of PG40 Core Protein," see also Figure 2). Krusius and Ruoslahti also teach that there are three Ser-Gly dipeptide sequences. A glycosaminoglycan chain is attached to one such serine, the one at position 4. There are also three glycosylation sites for possible N-glycosidic substitution (page 7686, first column, first paragraph under "Properties of the PG40 Core Polypeptide"). While Krusius and Ruoslahti teach the amino acid sequence in which a glycosaminoglycan chain is attached, Mann et al. (1990, JBC, 265: 5317-5323) teach that when serine 4 of decorin is mutated to theonine, the threonine-sbustituted decornin had a molecular weight similar to that of decorin core protein. The threonine mutant also did not bind to a DEAE-Sephadex column under the same conditions as the wild type protein. These results suggested that the glycosamineglycan attachment was eliminated (page 5320, first column, second paragraph, lines 1-7).

Roberts et al. (1992, Gene, 121: 255-262) teach that the goat beta-casein gene encodes the most abundant protein of goat milk (Roberts et al., abstract, line 1). Roberts et al. teach the sequence of goat-beta casein gene. Roberts et al. teach that transgenic mice comprising the 18.5 kb fragment containing the entire goat beta-casein gene were made. Compared to transgenic mice comprised of a rat beta-casein gene, the mice expressing the goat beta-casein gene expressed the goat gene consistently higher than the rat counterpart. Roberts et al. had considered that there may have been

locus-dependent effects that could account for the disparity in performance of the two genes (Roberts et al., page 260, col. 2, 3rd parag. lines 15-16). However, taking into consideration the number of different transgenic lineages of mice made with the rat and goat transgene, Roberts et al. did not think this was the case (Roberts, et al. page 260, col. 2, 3rd parag. lines 13-15).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express high levels of decorin that lacked GAG in the milk of a mammal, in the method taught by Houdebine et al.

One having ordinary skill in the art would have been motivated to make a transgenic construct comprising the goat beta-casein promoter, operatively link the promoter to a nucleotide sequence encoding human decorin, wherein serine at position 4 has been substituted to threonine, and inject the transgenic construct into mice, in order to obtain a mouse that expressed decorin that lacked GAG.

There would have been a reasonable expectation of success given the results of Houdebine et al. teaching a method of producing large amounts of active protein in milk, Mann et al. teaching that substituting serine for threonine at amino acid site 4 resulted in a decorin with no GAG chain, and Roberts et al. for teaching that mice comprised of the 18.5kb goat beta-casein transgene expressed at higher levels than mice comprised of the rat beta-casein transgene.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

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PRIMARY EXAMINER